REMARKS

Claims 34, 40 and 45-74 are pending in this application. By this amendment, claims 69 and 70 have been amended. Claims 71-74 have been previously withdrawn from consideration. Claims 34, 40, and 45-70 are currently under examination.

RCE

This response is being filed in response to the outstanding office action and in satisfaction of the submission requirement of the accompanying Request for Continued Examination (RCE).

Power of Attorney

File concurrently herewith is a Power of Attorney appointing the attorneys of customer number 35133 as the attorneys of record for the case.

Interview

Applicants note with appreciation the courtesies extended to their representatives, Melody Clark and Michael A. Patané, during the July 5, 2006 telephonic interview with Examiners Zachary Howard and Gary Nickol. The outstanding Office Action dated January 10, 2006 was discussed.

In particular, Applicants presented proposed amendments to claims 69 and 70. Examiner Howard indicated that the amendments will overcome the utility rejections under 35 U.S.C. § 101. The rejections under 35 U.S.C. § 112 for enablement and written description were also discussed, as was the rejection under 35 U.S.C. § 102. Although no agreement was reached, Applicants note with appreciation the Examiner's indication that he will re-evaluate each of the rejections in light of the interview and the reasoning set forth herein. The discussion below is consistent with the interview.

Claim Amendments

Applicants hereby amend claims 69 and 70. Support for the amendment can be found throughout the specification, for example, on page 34, lines 2-12. Page 34 lines 2-12 indicate that through tissue scans and other methods an orphan GPCR can be correlated to a disease or

disorder. Particularly, the specification notes that receptors can be localized to regions of organs and that based on the known functions of specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced. Applicants respectfully submit that no new matter has been introduced.

Additionally, the Examiner expressed some concern during the interview that the amendments might raise some written description issues. Although any such issues are not of record, Applicants respectfully submit that page 34, lines 2-12 of the specification describe correlation of orphan GPCRs to a disease or disorder, and thus there should not be any issues with written description.

Entry of the claim amendments is respectfully requested.

Claims Rejection 35 U.S.C. § 101

Claims 34, 40, and 45-70 stand rejected under 35 U.S.C. § 101 for allegedly lacking utility. Page 3 of the Office Action states:

> the utility rejection is based on the limitation in the claims that reads, 'wherein a location of the expression of said endogenous GPCR in a mammalian tissue source is known and said endogenous GPCR has been correlated with at least one mammalian physiological function.' The phrase 'correlated with at least one mammalian physiological function' broadly encompasses any GPCR wherein only the mammalian tissue source is known.

Applicants have amended the claims herein to delete the referenced language in favor of the phrase "wherein said endogenous GPCR can be associated with a disease or disorder". Support for the amendment can be found throughout the specification, for example, on page 34, lines 2-12. Applicants note with appreciation the Examiner's indication during the interview that the amendment will overcome the utility rejection.

Applicants respectfully assert that the amendments made herein are being made solely to facilitate prosecution of the application. Applicants maintain that the prior claims satisfied the

utility requirements, and present here for the record, arguments consistent with those made during the interview.

Although Applicants maintain that the Office has yet to provide evidence sufficient to support a *prima facie* case of lack of utility, we note that given Applicants' prior response, the Office must assess utility in light of the totality of the record. MPEP § 2107 directs that

> **Only** where the **totality of the record** continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained. (Emphasis added.)

The Office must establish that it is more likely than not that a person of ordinary skill in the art would not consider the utility asserted by Applicants to be specific and substantial. Applicants respectfully assert that the totality of the record shows that those of skill in the art would have been more likely than not to consider Applicants' utility to be specific and substantial.

Applicants' maintain that the original rejection did not satisfy the requirements for a *prima facie* showing of a lack of utility. MPEP § 2107.02 III.A. makes it clear that the Office must presume that Applicants' statements of utility are true, and that the Office should give deference to Applicants' understanding of the invention when the statements of utility are examined. The MPEP specifically states "Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. This can be done by simply evaluating the logic of the statements made, taking into consideration any evidence cited by the applicants." "Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons."

Furthermore, the MPEP § 2107.02 III.A continues, stating "to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e. "question") the truth of the statement of utility. The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Thus, to uphold the rejection, the totality of the evidence must show that it is more likely than not that Applicants' statements of utility are false.

Applicants respectfully assert that the totality of the evidence demonstrates a specific, substantial and credible utility and the Office has not provided evidence that it is more likely than not that Applicants' statements of utility are false.

The specification and the Watson Declaration (already of record) clearly indicate that those of skill in the art, at least at the time of filing, could associate a GPCR with a disease or disorder through studying and discovering the tissues where the GPCR is expressed, where the function of those tissues is known through routine methods known to those of skill in the art. Indeed, Dr. Watson states in paragraph 14 of his Declaration, that

> it is the location (e.g., cell or tissue type) of the receptor that is more telling to [the understanding of the putative function of the receptor], and not just its endogenous ligand.

Thus, those of skill in the art armed with expression data for a given GPCR could correlate that receptor to a physiological function and an associated disease or disorder. The Office has not provided any factual evidence to show that one skilled in the art would doubt this statement. Accordingly, the Office **must** accept Dr. Watson's comments, which clearly indicate that where the tissue expression of a GPCR is known, the GPCR can readily be correlated to a physiological function and associated diseases or disorders.

The Action recognizes the utility of exemplary GPCRs 19AJ, 19Y, 18A, and 18AI, as pointed out in the Watson Declaration. These GPCRs can be, and have been, correlated to certain diseases and disorders via their expression data. Although the Action attempts to distinguish these based on their facts, it remains clear that the totality of the evidence, including the Watson Declaration, demonstrates that those of skill in the art would have no reason to question the statements made by the Applicants in support of their utility. The record, herein, supported by Dr. Watson's Declaration, demonstrate Applicants' position that those of skill in the art, armed with expression data could correlate an orphan GPCR with a disease state, and that the GPCRs could then be useful in identifying candidate compounds for treating that disease state.

Dr. Watson's Declaration continues, at paragraph 22.a.1(a) stating that:

> In my scientific opinion, the location of a GPCR, by coupling this cellular location within specific cells, circuits, and organs, strongly links that GPCR to its physiological function...

Applicants' specification sets forth several GPCRs and their locations of expression thus, in Dr. Watson's words, strongly linking that GPCR to its physiological function – and, thus, to diseases or disorders associated with that tissue and function. Thus, where the physiological function of a tissue is known, and it is known that an orphan GPCR is expressed in that tissue, those of skill in the art can readily correlate that orphan GPCR with a disease or disorder of that tissue. Accordingly, a candidate compound found via the claimed methods would be expected to be useful in treating such a disease or disorder.

Applicants' specification, the reasoning presented herein and previously, coupled with the Watson Declaration and simple logic clearly show that one skilled in the art, in possession of the expression data for an orphan GPCR would readily correlate that GPCR with a mammalian tissue, physiological function, and an associated disease or disorder. Thus, the claimed methods of identifying candidate compounds have utility. The Office has not provided any factual evidence showing that one skilled in the art would question Dr. Watson's statements or Applicants' conclusions. As such, the totality of the record does not make it more likely than not that one skilled in the art would doubt Applicants' utility. The presumption of utility, therefore, must stand, and the rejection should be withdrawn.

Solely to facilitate prosecution, Applicants have amended independent claims 69 and 70. As concluded at the interview, the amendments submitted herein will overcome the rejections under 35 U.S.C. § 101. Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 101.

35 U.S.C. § 112, 1st paragraph - Enablement

The rejection has two parts, the first concerns constitutive activation and the second concerns correlation with a physiological function.

Constitutive Activation

Claims 34, 40, and 45-70 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. This rejection was tied to the utility rejection, and, like the utility rejection, should be withdrawn.

The Action notes that even if a substantial utility were asserted, the claims would still lack enablement for failing to enable constitutive activation of orphan GPCRs by any mechanism other than those found in the specification. Applicants respectfully assert, as discussed during the interview, that the method of constitutive activation is not important, and that those of skill in the art would readily recognize and be able to implement any of a number of methods to produce constitutive activation. Applicants note with appreciation the Examiner's willingness to reconsider this rejection in light of the comments during the interview and noting that the rejection itself indicates that several of the disclosed methods are highly predictable (see Office Action page 8). Those of skill in the art would recognize that these and other methods could be used to produce a constitutively activated orphan GPCR. Accordingly, no undue experimentation is required. Withdrawal of the enablement rejection on these grounds is respectfully requested.

Correlation with physiological function

The amendments herein obviate this rejection because the rejection centers around the now deleted language concerning correlation of the orphan GPCR with a physiological function. Withdrawal of the rejection is respectfully requested.

35 U.S.C. § 112 - 1st Paragraph – Written Description

Claims 34, 40 and 45-70 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. As above, the rejection is actually in two parts, first dealing with constitutive activation and, second, with correlation to a physiological function.

Constitutive Activation

As noted above, Applicants respectfully assert that those of skill in the art would readily recognize that orphan GPCRs could be constitutively activated in any of a number of ways, and

thus were clearly in the possession of the inventors at the time of filing, since several of these methods are disclosed in the specification. As noted above, several of the methods have been recognized by the Office as predictable, and therefore clearly indicate that the inventors were in possession of the invention and could predictably constitutively activate orphan GPCRs. Withdrawal of the rejection is respectfully requested.

Correlation to a physiological function

The amendments herein obviate this rejection because the rejection centers around the now deleted language concerning correlation of the orphan GPCR with a physiological function. Withdrawal of the rejection is respectfully requested.

35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 40, 53, 55, 56, 58, 60, 68 and 70 under 35 U.S.C. §102(e) for alleged anticipation by Gershengorn et al. (U.S. Patent No. 6,087,115).

At the time of the Applicants' invention, constitutively active receptors were known in the art and it was known that such receptors can signal in the absence of a ligand. Orphan receptors were also known in the art at the time of the invention. However, it was not appreciated at the time of the invention that orphan receptors could be systematically screened by applying the concept of constitutive activation as claimed in the subject application.

The subject specification teaches that the traditional study of receptors has always proceeded from the *a priori* assumption that the endogenous ligand must first be identified before discovery could proceed to find antagonists and other molecules which could affect the receptor (see, for example, page 29, lines 13-17). The specification further teaches that this mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors (see page 29, lines 17-20). Applicants note that this is the case with the Gershengorn patent where in the first example they identify endogenous ligands that bind to the constitutively active KSHV recepor (see in particular col. 8, lines 1-30). Thus, the Gershengorn patent follows the dogma of the time period by identifying endogenous ligands for the receptor.

In the Office Action dated April 19, 2005, it was acknowledged that agonists are not present in the method of Gershengorn. In addition, the Office Action acknowledged that Gershengorn does determine several endogenous ligands that bind to the GPCR; however, under the 102 rejection section, the Office Action alleged that "this teaching does not detract from the obviousness of using a GPCR without first identifying a ligand in the general screening method taught by Gershengorn." Similarly, the present Office Action acknowledges that Gershengorn does not use the term orphan receptor. However, the Office Action alleges that the method taught by Gershengorn does not require that a ligand be identified for the receptor.

Applicants have argued, and continue to argue, that the Gershengorn reference does not teach each element of the claimed invention as is required for anticipation. MPEP section 2131 states "in order for a reference to anticipate a claim, the reference **must** teach each and every element of the claims" (emphasis added). Importantly, the Gershengorn reference does not teach the claimed element "wherein an endogenous ligand for said receptor has not been identified." Applicants respectfully assert that Gershengorn does not teach any orphan receptors and further does not teach that orphan receptors can be screened by applying the concept of constitutive activation.

The present Office Action indicates that the method taught by Gersengorn does not require that a ligand be identified for the receptor. Of course, the reference also does not teach that the ligand must not be known, as claimed by Applicant. Gershengorn is silent with respect to this point. Applicants note that at the time of filing (April 1997) those of skill in the art were accustomed to working with de-orphanized receptors, since the dogma of the day demanded de-orphanization prior to proceeding with any further work. Applicants' specification, not Gershengorn, teaches that orphan receptors can be the subject of screens prior to de-orphanizing the receptor. Applicants respectfully assert that whether or not a ligand is required for the method described by Gershengorn is irrelevant for novelty. Regardless of whether the ligand was required for the Gershengorn method, the methods disclosed were applied only to a receptor with a known ligand, i.e. after the receptor was deorphanized. This is in sharp contrast to Applicants' claimed invention which requires that the ligand be unidentified. The Gershengorn

patent simply does not teach the method claimed by the subject application which clearly requires that the receptor is an orphan receptor (i.e., an endogenous ligand for the receptor has *not* been identified).

The present Office Action also incorrectly states that "at the time of filing of the Gershengorn patent application, the ligand for KSHV was not known." In fact, it was known by Gershengorn and is disclosed in the patent application on the filing date (January 22, 1997). As discussed with the Examiner in the interview on July 5, 2006, Applicants note that one of the inventors on the Gershengorn patent, Ethel Cesarman, is the first author on a paper published in the Journal of Virology in November 1996 (two months prior to the filing date of the Gershengorn patent) attached herewith as Exhibit A. The Cesarman et al. paper discloses that KSHV has the closest homology to IL-8 receptors and the closest viral homology is to a receptor that as been shown to be a functional IL-8 receptor. They conclude "Thus it is likely that the KSHV GPCR may function as a chemokine receptor" (see page 8221, column 2, second full paragraph). Indeed, the Gershengorn patent discloses the IL-8 chemokine as an endogenous ligand for the KSHV receptor (see column 8, lines 15-30). Thus, the methods of Gershengorn were conducted on the de-orphanized KSHV, and there simply is no teaching or suggestion that Gershengorn intended, or that those of skill in the art would have recognized, that such methods be applied to orphan receptors.

Finally, Applicants note that if Gershengorn had been in possession of the Applicants invention (which Applicants adamantly argue is not the case) they would not have taken the time to first determine a ligand that binds to the KSHV receptor as shown in Example 1. There is simply no teaching in the Gershengorn application of a method for screening orphan receptors by applying the concept of constitutive activation as claimed in the subject application. Applicants submit that the Office Action has impermissibly used hindsight in formulating the novelty rejection.

In conclusion, the requirements for anticipation have not been met by the Gershengorn patent. Specifically, the Gershengorn patent does not teach the claim element "wherein an endogenous ligand for said receptor has not been identified" (an orphan receptor) and does not

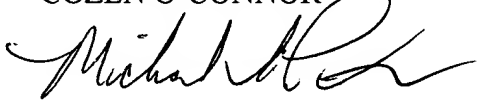
teach a method of screening orphan receptors utilizing constitutive activation as claimed in the subject application. Because the Gershengorn reference does not teach each and every element of the claimed invention, the reference can not anticipate the claimed invention. Therefore, Applicants request that this ground of rejection be withdrawn.

The Commissioner is hereby authorized to charge any fee or underpayment thereof or credit any overpayment to deposit account no. 50-1275.

Early reconsideration and allowance of all pending claims is respectfully requested. The examiner is requested to contact the undersigned attorney if an interview, telephonic or personal, would facilitate allowance of the claims.

Respectfully submitted,

COZEN O'CONNOR



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